97N-0217

NAA
NATIONAL AQUACULTURE ASSOCIATION
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September 2, 1997

Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Drive, Room 1-23
Rockville, MD 20857

SUBJECT: Request for Comments on Development of Options to Encourage Animal Drug Approvals for Minor Species and for Minor Use (Docket No. 97N-0217)

97 SEP -5 P1 :45

The National Aquaculture Association (NAA) wishes to comment on "Development of Options to Encourage Animal Drug Approvals for Minor Species and for Minor Use." The following comments were compiled by Rosalie Schnick, National Coordinator for New Animal Drug Applications with input from our members, which include all the major aquaculture organizations, as well as individual producers on this topic.

A. Scope--Criteria for the determination of a minor species or a minor use

Comments: In the case of food animals, the criteria for determining whether the species is a minor species should be based on a per capita consumption rate that is based only on domestically farmed animals. No imported or captured animals would count toward determination of per capita consumption since neither the U.S. Food and Drug Administration (FDA) nor Center for Veterinary Medicine (CVM) has no control over the use of drugs in these animals.

B. Creating Additional Statutory Authority

1. Should there be different standards for target animal safety and effectiveness of new animal drugs intended for use in minor species or for minor uses? Should there be different standards for human food safety for new animal drugs intended for minor species or for minor uses?

Comments: The standards should be different for target animal safety and effectiveness of new animal drugs intended for use in minor species or for minor uses. There are other effective methods

111 West Washington Street, Suite 1
Charles Town, WV 25414-1529
800/626-3301 • 304/728-2167
Fax: 304/728-2196 • e-mail: naa@intrepid.net

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available (e.g., marketplace determinations) that can demonstrate animal safety and drug effectiveness. The human food safety standards for drugs intended for use on food animals identified as minor species must provide data that demonstrates that the food is safe for human consumption; however, the methods and tests used to provide this assurance may be different from those required for major food species.

2. If so, what should those standards be?

Comments: In the case of target animal safety and effectiveness standards, the principle should be "Let the marketplace decide." If a product is proven safe and effective for use in one species to control a certain disease, the producers will buy the product. Thus, minimal data should be required. For antibacterials, demonstration of an *in vitro* minimum inhibitory concentration should be sufficient for efficacy prior to marketplace examination. "Flexible labeling"should be used to allow for the broadest listing of species and diseases, where groups of animals (e.g., classes of fish) and diseases can be placed on the label and where a range of doses or concentrations is acceptable to one dose or concentration. In addition, there should be no need to establish an "optimum dose or concentration" since the labeling would allow a range based on a variety of sources of data and information.

Sufficient target animal safety data and information may be available in the literature or from other countries even though the studies may not have been completed under "Good Laboratory Practices" provisions. If there are no acceptable data available in the literature or from other countries, one target animal safety study should be sufficient to cover "all fish" by using a flexible study design with the most sensitive representative species that has been determined by a pilot study or historical information.

Additionally, FDA should expand the Veterinary Feed Directive program outlined in AMDUCA to allow for extra-label use of medicated feeds. FDA should endorse the program outlined in the Minor Animal Species Health Coalition response scheduled for submission in this docket No. 97N-0217. This program could be used to gather data on efficacy and target animal safety under a variety of environmental conditions.

Concerning human food safety, there is a need to accept the definition and concept of non-food fish for all early life stages (gametes, eggs, fry, fingerlings) and broodstock, and not on a case-by-case basis of early life stages. We feel that all early life stages of all fish have a long inherent withdrawal time that guarantees that no residues from drugs used on these life stages will enter the human food supply. Enough data have been generated on drug metabolism and tissue residue distribution and depletion in fish that CVM should not be concerned about any residues being available to humans under these uses. The public and private aquaculture industry needs to define the size of fingerlings for each species so that CVM can incorporate this life stage into the definition. Inclusion of broodstock in the non-food definition would mean that no broodstock would ever enter the human food supply.

The human food safety standards should have a consumption factor in its calculations in which only consumption data for the domestically farmed animals is used. In addition, CVM, who has encouraged crop grouping research, needs to review the research data on the concept, accept a range of variations in response to the drugs researched in pharmacokinetic studies, and require only one set of residue chemistry studies per drug. The use of surrogate species to reduce costs and, at the same time, providing for human food safety is extremely important to increasing the number of approved drugs for aquaculture. There is a need for CVM to recognize the safety of those drugs that have a long history of safe use in aquaculture, especially those drugs that are considered to be Generally Recognized as Safe (GRAS); no additional safety studies should be required to add aquaculture drug uses to GRAS drugs.

If there is a concern for human food safety (e.g., drug resistance in humans from animal sources) from the use of drugs in minor species, then FDA should accept risk assessments by experts that factor in culture practices, consumption figures, and built-in controls (e.g., post-approval monitoring).

3. Should the standards be the same for all minor species or uses? Why?

Comments: There should be no difference in the standards for any minor species of aquatic animals except for the provision that there are aquatic animals that should be regarded as non-food animals (e.g., aquarium fish, bait fish, all early life stages of all fish, broodfish) and subject to reduced stringency of drug approvals. For example, there should be no need for residue chemistry studies for any fish species or life stage defined as non-food. If the recommendations made in this letter for development of efficacy and target animal safety data are accepted and implemented by CVM, there is no need to have separate standards for any aquatic animals. However, if these recommendations are not accepted, then there needs to be different standards for generating efficacy and target animal safety data for aquarium fish and bait fish.

4. How would appropriate doses be determined and how would residue depletion and withdrawal times for food animals be determined?

Comments: Effectiveness data for water borne treatments, particularly to treat body surface pathogens, could be gained from information in the literature, data from other countries, testimony from experts, or from a single pivotal efficacy study so that all fish could be included on the label claim. The fish is merely a substrate for the external pathogen. In the case of oral drugs, a dosage could also be determined from the scientific literature or from data generated on a dosage from other countries. In the absence of this information, one pivotal efficacy study should be sufficient for fish. The controls used in the efficacy studies could be actual positive and negative controls, historical data, or testimony by experts. Efficacy data and reviews of those data from other countries should be replacements for studies done in this country if the data and reviews are sound.

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Comments: The primary review process could be accomplished by a panel of industry and government participants external to the agency. CVM should pay for these reviews, but industry would have to support increased funding for CVM to do so. In fact, there is a need for expedited reviews of current drug applications that could benefit from a system such as this. Currently, every time new information is requested, CVM has another 90 days to respond. This situation is most discouraging to the pharmaceutical companies.

Again, if there could be a guarantee that the review process would be accelerated, the industry would support increased funding for CVM to do so through earmarking the funds for that purpose. If funding is not increased for CVM, then the users would have to come up with the needed funds through user fees or some form of funding mechanism to guarantee that reviews are accelerated.

8. Could determinations of animal safety and effectiveness by expert panels or compendia be used to support drug approvals for minor species and minor uses? If so, what information would serve as the basis for such determinations? Should the determinations of these panels or other information be used to issue monographs or similar standards? Who would draft monographs or similar standards and why?

Comments: Expert panels should be used to determine efficacy and animal safety for approvals of drugs for minor species and minor uses. Information from the literature and expert opinion could serve for such determinations. Monographs could be written by industry experts who have the background in that area of expertise. In the early 1970's, CVM considered this approach under "Not New Drug Monographs" but the agency never followed up on this approach. This mechanism would work today if CVM offered guidance in the preparation of the documents.

C. Administrative and Regulatory Changes

1. Should there be different standards for manufacturing of drugs for minor species or minor uses? If so, what should those standards be? Should products be labeled to reflect the use of different manufacturing standards?

Comments: There should be different standards for manufacturing of drugs for minor species and minor uses, especially for water borne drugs that are used in large quantities as compared to drugs administered in medicated feed or injected. These standards should be determined by a panel of manufacturers and CVM and these standards should be reflected on the product label.

2. Would a strategy similar to that used by the agency to facilitate drug approvals for some aquatic species be successful if extended to other minor species?

Comments: Other minor species industries would benefit from the same program offered the aquaculture industry because progress is currently being made toward approvals. The aquaculture industry appreciates the efforts by CVM to provide for formal compassionate Investigational New Animal Drug (INAD) exemptions, formal Low Regulatory Priority status for certain drugs, and "flexible labeling."

D. Creating incentives

1. Would economic incentives, such as tax breaks, grants, and periods of market or label

exclusivity, encourage the pursuit of approvals or supplemental approvals for labeling modifications for minor species or minor uses? If so, what kinds of incentives would be most effective? Would different kinds of incentives be appropriate for different classes of new animal drugs?

Comments: Economic incentives would attract more pharmaceutical and chemical companies to the aquaculture industry. From our viewpoint, delayed taxation on profits for a period of years, creation of a classification of "orphan drugs"for minor species or minor uses, extensions of the current periods of exclusivity, and criteria for determining how exclusivity is granted, should be implemented by Congress. As we understand, CVM would like to offer longer periods of exclusivity but the agency cannot do anything until Congress changes the laws. The periods of time should be at least 10 years for a new NADA and seven years for a supplemental NADA.

2. What incentives would encourage sponsors to pursue approval of a drug for a minor species or for a minor use using data in public master files (PMF's)? Are there concerns about data in PMF's that make new animal drug sponsors reluctant to rely on such data? What are those concerns?

Comments: Changing the criteria for qualifying for exclusivity would be one incentive that would encourage sponsors to pursue approval of minor species drugs using a PMF. This would involve allowing the company to qualify for exclusivity without having to perform or fund an efficacy study as they currently do; if a company is willing to step forward and become an NADA sponsor, they should have to do it with minimal effort. There may be other criteria for qualifying for exclusivity that could be changed to attract sponsors.

We understand that one of the concerns of the pharmaceutical companies is liability. If companies could somehow be protected from litigation via labeling, then sponsors would be more willing to use the data from PMFs. Placing a warning on the label that the use of this drug on species with little or no data is done at the risk of the user would be one way of removing the concerns of the sponsor.

Some of the other items mentioned above should offer incentives to sponsors. These would include broad labels that include all fish and more than one disease claim, target animal safety and residue chemistry studies on one surrogate species, and minimal product chemistry requirements. One item, not been addressed above but an important factor in aquaculture drug approvals, is the data required for environmental safety determinations. Currently, the regulations do not exempt aquaculture from generating environmental data by categorical exclusions as Animal Drug Availability Act of 1996 did for terrestrial animal production; this situation needs to be changed.

3. If producer groups or other organizations were willing to conduct or otherwise fund studies to demonstrate safety and efficacy for new animal drug approvals for minor

species or minor uses, would sponsors be willing to use the data from the studies to support approvals and new or revised labeling? If not, why not?

Comments: The aquaculture industry has demonstrated that sponsors have a greater interest in coming forward if other groups have developed safety and efficacy data at no expense to the sponsor. More sponsors might become interested if an organized effort was made to make the sponsors aware of the advantages of this route of approval.

4. Should a program similar to the U.S. Department of Agriculture's National research Support Program # 7 (NRSP-7), which currently funds studies for minor use therapeutic uses for food- and fiber-producing animals, be developed for wildlife and zoo animals and/or for production uses?

Comments: No new program should be developed; rather, the NRSP-7 program should be expanded to include drugs for non-food fish and for production uses such as spawning and gender manipulation aids. These drugs are critical to the production of certain fish species (e.g., hybrid striped bass, tilapia).

5. Could and should philanthropic, public interest, or other not-for-profit organizations be encouraged to fund research for the development of new animal drugs intended for use in minor species or for minor uses? If so, how, and by whom?

Comments: Philanthropic, public interest, or other not-for-profit organizations should be encouraged to fund research for the development of new animal drugs intended for use in minor species or for minor uses. This encouragement would come from a coordinated effort from the industry and CVM that would involve education and delineation of the benefits.

6. Are there mechanisms other than the new animal drug approval process and extralabel uses of animal and human drugs under the AMDUCA that could enhance drug availability for minor species and for minor uses?

Comments: Low Regulatory Priority (LRP) rulings could be extended on a case-by-case basis beyond the current listing of drugs and their uses in aquaculture to include safe drugs not currently considered LRP and to include more uses of current LRP drugs. There is a need for CVM to extend the Generally Recognized as Safe status to aquaculture use for those drugs that have a long history of safe use in aquaculture without requiring additional studies on aquatic species to confirm the efficacy and safety of that drug.

As previously mentioned, two mechanisms would greatly enhance drug availability for minor species and for minor uses. One mechanism is the use of the crop grouping concept for all data requirements because it would reduce the cost of drug development and the time needed to generate the data. The other mechanism, a general non-food fish

definition for all gametes, eggs, fry, fingerlings (as defined by the aquaculture industry), and broodstock, would eliminate the need for residue chemistry data, data that are very expensive and time-consuming to generate.

Another mechanism to enhance drug availability for minor species or minor uses could be through equivalency agreements with other countries. The FDA must, for food safety purposes, determine whether the food safety program of another country is equivalent to the United States. During this process, FDA must examine whether drugs used by aquaculturists in other countries are likely to leave violative residues. If the country passes the equivalency test, drugs legitimately used in that country should be available to U.S. producers under similar requirements.

E. Extending existing legal authority

1. Would legislation be desirable to extend the AMDUCA to permit extralabel use of: (1) medicated feeds or (2) reproductive hormones and implants? What are the pros and cons of approval versus extralabel use under the AMDUCA?

Comments: The NAA supports a program whereby FDA would state in its Compliance Policy Guide (CPG) that the use of certain spawning aids administered by immersion, injection, implantation, or feed and any approved therapeutants administered in medicated feed for control or prevention of diseases in unapproved minor species is a matter of enforcement discretion and not a matter of regulatory concern. The CPG would list specific drugs, minor species uses, use levels, withdrawal times, and other relevant details that ordinarily would not be of regulatory concern. CVM's decision to list specific drugs and conditions of use in the CPG would be based on its review of drug monographs prepared by the U.S. Pharmacopeial Convention, extrapolation of drug approval data, published literature, unpublished data and information submitted to CVM by producer organizations, veterinarian associations, drug sponsors, academicians and others. Additional details of this proposal will be submitted under separate cover by the Minor Species Animal Health Coalition.

Thank you for the opportunity to comment on the legislative and regulatory options to facilitate the approval of new animal drugs intended for use in minor species or for minor uses. The NAA hopes that aquaculture drug approvals will be increased through implementation of these options.

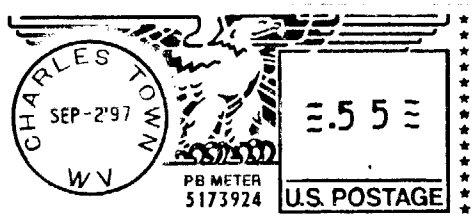
Sincerely,

Jim Ekstrom

Jim Ekstrom
President

JE:mw

NAA
NATIONAL AQUACULTURE ASSOCIATION
ONE INDUSTRY • ONE VOICE
111 West Washington Street, Suite 1
Charles Town, WV 25424-1529



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